
CHAPTER 8

RISK CHARACTERIZATION

This chapter describes the final step of the baseline health risk assessment process, risk characterization. In this step, the toxicity and exposure assessments are summarized and integrated into quantitative and qualitative expressions of risk. To characterize potential noncarcinogenic effects, comparisons are made between projected intakes of substances and toxicity values; to characterize potential carcinogenic effects, probabilities that an individual will develop cancer over a lifetime of exposure are estimated from projected intakes and chemical-specific dose-response information. Major assumptions, scientific judgments, and to the extent possible, estimates of the uncertainties embodied in the assessment are also presented.

Risk characterization also serves as the bridge between risk assessment and risk management and is therefore a key step in the ultimate site decision-making process. This step assimilates risk assessment information for the risk manager (RPM or regional upper management involved in site decision-making) to be considered alongside other factors important for decision-making such as economics, technical feasibility, and regulatory context. The risk characterization methods described in this chapter are consistent with EPA's published risk assessment guidelines. Exhibit 8-1 is an overview of risk characterization, and illustrates how it relates to the preceding toxicity and exposure assessments and to the following development of preliminary remediation goals.

In the following sections, the risk characterization methodology is described. There are separate discussions for carcinogenic and noncarcinogenic effects because the methodology differs for these two modes of chemical toxicity. In addition to giving instructions for calculating numerical estimates of risk, this chapter provides guidance for interpreting, presenting, and qualifying the results. A risk characterization

cannot be considered complete unless the numerical expressions of risk are accompanied by explanatory text interpreting and qualifying the results.

8.1 REVIEW OF OUTPUTS FROM THE TOXICITY AND EXPOSURE ASSESSMENTS

Most sites being assessed will involve the evaluation of more than one chemical of concern and might include both carcinogenic and noncarcinogenic substances. The first step in risk characterization is to gather, review, compare, and organize the results of the exposure assessment (e.g., intakes for all exposure pathways and land-uses and for all relevant substances) and toxicity assessment (e.g., toxicity values for all exposure

ACRONYMS FOR CHAPTER 8

ARAR = Applicable or Relevant and Appropriate Requirement
ATSDR = Agency for Toxic Substances and Disease Registry
CDI = Chronic Daily Intake
ECAO = Environmental Criteria and Assessment Office
E = Exposure Level
HI = Hazard Index
IRIS = Integrated Risk Information System
LOAEL = Lowest-Observed-Adverse-Effect-Level
NOAEL = No-Observed-Adverse-Effect-Level
NRC = Nuclear Regulatory Commission
RfD = Reference Dose (when used without other modifiers, RfD generally refers to chronic reference dose)
RfD_{at} = Developmental Reference Dose
RfD_s = Subchronic Reference Dose
RI/FS = Remedial Investigation/Feasibility Study
RME = Reasonable Maximum Exposure
SDI = Subchronic Daily Intake
SF = Slope Factor

DEFINITIONS FOR CHAPTER 8

Absorbed Dose. The amount of a substance penetrating the exchange boundaries of an organism after contact. Absorbed dose is calculated from the intake and the absorption efficiency. It usually is expressed as mass of a substance absorbed into the body per unit body weight per unit time (e.g., mg/kg-day).

Administered Dose. The mass of substance given to an organism and in contact with an exchange boundary (e.g., gastrointestinal tract) per unit body weight per unit time (e.g., mg/kg-day).

Chronic Reference Dose (RfD). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime. Chronic RfDs are specifically developed to be protective for long-term exposure to a compound (as a Superfund program guideline, seven years to lifetime).

Developmental Reference Dose (RfD_d). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of an exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of development effects. Developmental RfDs are used to evaluate the effects of a single exposure event.

Exposure. Contact of an organism with a chemical or physical agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut) and available for absorption.

Exposure Assessment. The determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure.

Exposure Pathway. The course a chemical or physical agent takes from a source to an exposed organism. An exposure pathway describes a unique mechanism by which an individual or population is exposed to chemicals or physical agents at or originating from a site. Each exposure pathway includes a source or release from a source, an exposure point, and an exposure route. If the exposure point differs from the source, a transport/exposure medium (e.g., air) or media (in cases of intermedia transfer) also is included.

Exposure Route. The way a chemical or physical agent comes in contact with an organism (e.g., by ingestion, inhalation, dermal contact).

Hazard Index (HI). The sum of more than one hazard quotient for multiple substances and/or multiple exposure pathways. The HI is calculated separately for chronic, subchronic, and shorter-duration exposures.

Hazard Quotient. The ratio of a single substance exposure level over a specified time period (e.g., subchronic) to a reference dose for that substance derived from a similar exposure period.

Intake. A measure of exposure expressed as the mass of a substance in contact with the exchange boundary per unit body weight per unit time (e.g., mg chemical/kg body weight-day). Also termed the normalized exposure rate; equivalent to administered dose.

Integrated Risk Information System (IRIS). An EPA data base containing verified RfDs and slope factors and up-to-date health risk and EPA regulatory information for numerous chemicals. IRIS is EPA's preferred source for toxicity information for Superfund.

Reference Dose (RfD). The Agency's preferred toxicity value for evaluating noncarcinogenic effects result from exposures at Superfund sites. See specific entries for chronic RfD, subchronic RfD, and developmental RfD. The acronym RfD, when used without other modifiers, either refers generically to all types of RfDs or specifically to chronic RfDs; it never refers specifically to subchronic or developmental RfDs.

Slope Factor. A plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime. The slope factor is used to estimate an upper-bound probability of an individual developing cancer as a result of a lifetime of exposure to a particular level of a potential carcinogen.

Subchronic Reference Dose (RfD). An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a portion of a lifetime (as a Superfund program guideline, two weeks to seven years).

Weight-of-Evidence Classification. An EPA classification system for characterizing the extent to which the available data indicate that an agent is a human carcinogen. Recently, EPA has developed weight-of-evidence classification systems for some other kinds of toxic effects, such as developmental effects.

routes and relevant substances). The following two subsections describe how to organize the outputs from the exposure and toxicity assessments and how to check for the consistency and validity of the information from the preceding exposure and toxicity assessments.

8.1.1 GATHER AND ORGANIZE INFORMATION

For each exposure pathway and land-use evaluated in the exposure assessment, check that all information needed to characterize risk is available. The necessary exposure information is outlined in the box below.

EXPOSURE INFORMATION NEEDED FOR RISK CHARACTERIZATION

- Estimated intakes (chronic, subchronic, and shorter-term, as appropriate) for chemicals.
- Important exposure modeling assumptions, including:
 - chemical concentration at the exposure points;
 - frequency and duration of exposure;
 - absorption assumptions; and
 - characterization of uncertainties.
- List of which exposure pathways can reasonably contribute to the exposure of the same individuals over the same time period.

For each chemical or substance evaluated in the toxicity assessment, use the checklist provided in the box below to ensure that all information needed to characterize risk is available.

8.1.2 MAKE FINAL CONSISTENCY AND VALIDITY CHECK

Check the consistency and validity of key assumptions common to the exposure outputs and the toxicity outputs for each contaminant and exposure pathway of concern. These assumptions include the averaging period for exposure, the exposure route, and the absorption adjustments. The

TOXICITY INFORMATION NEEDED FOR RISK CHARACTERIZATION

- Slope factors for all carcinogenic chemicals.
- Discussion of weight of evidence and classifications for all carcinogenic chemicals.
- Type of cancer for Class A carcinogens.
- Chronic and subchronic RfDs and shorter-term toxicity values (if appropriate) for all chemicals (including carcinogens and developmental toxicants).
- Critical effect associated with each RfD.
- Discussion of uncertainties, uncertainty factors, and modifying factor used in deriving each RfD and "degree of confidence" in RfD (i.e., high, medium, low).
- Whether the toxicity values are expressed as absorbed or administered doses.
- Pharmacokinetic data that may affect the extrapolation from animals to humans for both the RfD and slope factor.
- Uncertainties in any route-to-route extrapolations.

basic principle is to ensure that the exposure estimates correspond as closely as possible with the assumptions used in developing the toxicity values.

Averaging period for exposure. If the toxicity value is based on average lifetime exposure (e.g., slope factors), then the exposure duration must also be expressed in those terms. For estimating cancer risks, always use average lifetime exposure; i.e., convert less-than-lifetime exposures to equivalent lifetime values (see EPA 1986a, *Guidelines for Carcinogen Risk Assessment*). On the other hand, for evaluating potential noncarcinogenic effects of less-than-lifetime exposures, do not compare chronic RfDs to short-term exposure estimates, and do not convert short-term exposures to equivalent lifetime values to compare with the chronic RfDs. Instead, use subchronic or shorter-term toxicity values to evaluate short-term exposures. Check that the estimated exposure duration is sufficiently similar to the duration of the exposure in the study used to identify the toxicity value to be protective of human health (particularly for subchronic and shorter-term

effects). A toxicologist should review the comparisons. In the absence of short-term toxicity values, the chronic RfD may be used as an initial screening value; i.e., if the ratio of the short-term exposure value to the chronic RfD is less than one, concern for potential adverse health effects is low. If this ratio exceeds unity, however, more appropriate short-term toxicity values are needed to confirm the existence of a significant health threat. ECAO may be consulted for assistance in finding short-term toxicity values.

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Exposure route. Check that all toxicity values used for each exposure pathway being evaluated at the site are consistent with the route of exposure (e.g., oral to oral, inhalation to inhalation). It is not possible to extrapolate between exposure routes for some substances that produce localized effects dependent upon the route of exposure. For example, a toxicity value based on localized lung tumors that result only from inhalation exposure to a substance would not be appropriate for estimating risks associated with dermal exposure to the substance. At this time, EPA considers it appropriate only to extrapolate dermal toxicity values from values derived for oral exposure. It is not recommended that oral toxicity reference values be extrapolated casually from inhalation toxicity values, although this extrapolation may be performed on a case-by-case basis in consultation with ECAO. In general, inhalation values should not be extrapolated from oral values. See Section 7.5.1 for additional information.

Inhalation RfD_i values obtained from IRIS will usually be expressed as ambient air concentrations (i.e., mg/m³), instead of as administered doses (i.e., mg/kg-day). It may be necessary, therefore, to calculate the RfD_i in units of mg/kg-day for comparison with the intake estimated in the exposure

assessment. The RfD_i expressed in mg/kg-day would be equal to the RfD_i in mg/m³ multiplied by 20 m³ air inhaled per person per day divided by 70 kg per person.

Absorption adjustment. Check that the exposure estimates and the toxicity values are either both expressed as absorbed doses or both expressed as intakes (i.e., administered doses). Except for the dermal route of exposure, the exposure estimates developed using the methods provided in Chapter 6 should be in the form of intakes, with no adjustments made for absorption. However, there are three types of absorption adjustments that might be necessary or appropriate depending on the available toxicity information. These are described below. Sample calculations for these absorption adjustments are provided in Appendix A.

- (1) Dermal exposures. The output of the exposure assessment for dermal exposure is expressed as the amount of substance absorbed per kg body weight per day. It therefore may be necessary to derive an absorbed-dose toxicity value from an administered-dose toxicity value to compare with the exposure estimate. See Appendix A for sample calculations.
- (2) Absorbed-dose toxicity value. For the substances for which the toxicity value is expressed as an absorbed rather than administered dose (e.g., inhalation slope factor in IRIS for trichloroethylene and several other substances), one should express exposure as an absorbed dose rather than as an intake. See Appendix A.
- (3) Adjustment for medium of exposure. Adjusting for different absorption efficiencies based on the medium of exposure (e.g., food, soil, or water for oral exposure, water or particulates for inhalation exposure) is occasionally appropriate, but not generally recommended unless there are strong arguments for doing so. Many oral RfD and slope factor values assume ingestion in water even when based on studies that employed administration in corn oil by gavage or in feed. Thus, in most cases, the unadjusted toxicity value will provide a

reasonable or conservative estimate of risk. See Appendix A.

8.2 QUANTIFYING RISKS

This section describes steps for quantifying risk or hazard indices for both carcinogenic and noncarcinogenic effects to be applied to each exposure pathway analyzed. The first subsection covers procedures for individual substances, and is followed by a subsection on procedures for quantifying risks associated with simultaneous exposures to several substances. Sample table formats for recording the results of these calculations as well as recording associated information related to uncertainty and absorption adjustments are provided in Exhibits 8-2 through 8-4.

8.2.1 CALCULATE RISKS FOR INDIVIDUAL SUBSTANCES

Carcinogenic effects. For carcinogens, risks are estimated as the incremental probability of an individual developing cancer over a lifetime as a result of exposure to the potential carcinogen (i.e., incremental or excess individual lifetime cancer risk). The guidelines provided in this section are consistent with EPA's (1986a) *Guidelines for Carcinogen Risk Assessment*. For some carcinogens, there may be sufficient information on mechanism of action that a modification of the approach outlined below is warranted. Alternative approaches may be considered in consultation with ECAO on a case-by-case basis.

The slope factor (SF) converts estimated daily intakes averaged over a lifetime of exposure directly to incremental risk of an individual developing cancer. Because relatively low intakes (compared to those experienced by test animals) are most likely from environmental exposures at Superfund sites, it generally can be assumed that the dose-response relationship will be linear in the low-dose portion of the multistage model dose-response curve. (See the Background Document 2 of IRIS for a discussion of the multistage model). Under this assumption, the slope factor is a constant, and risk will be directly related to intake. Thus, the linear form of the carcinogenic risk equation is usually applicable for

estimating Superfund site risks. This linear low-dose equation is described in the box below.

LINEAR LOW-DOSE CANCER RISK EQUATION

$$\text{Risk} = \text{CDI} \times \text{SF}$$

where:

Risk	=	a unitless probability (e.g., 2×10^{-5}) of an individual developing cancer;
CDI	=	chronic daily intake averaged over 70 years (mg/kg-day); and
SF	=	slope factor, expressed in (mg/kg-day) ⁻¹ .

The CDI is identified in Exhibits 6-11 through 6-19 and 6-22 and the SF is identified in Exhibit 7-3.

However, this linear equation is valid only at low risk levels (i.e., below estimated risks of 0.01). For sites where chemical intakes might be high (i.e., risk above 0.01), an alternate calculation equation should be used. The one-hit equation, which is consistent with the linear low-dose model given above and described in the box on page 8-11, should be used instead.

Because the slope factor is often an upper 95th percentile confidence limit of the probability of response based on experimental animal data used in the multistage model, the carcinogenic risk estimate will generally be an upper-bound estimate. This means that EPA is reasonably confident that the "true risk" will not exceed the risk estimate derived through use of this model and is likely to be less than that predicted.

Noncarcinogenic effects. The measure used to describe the potential for noncarcinogenic toxicity to occur in an individual is not expressed as the probability of an individual suffering an adverse effect. EPA does not at the present time use a probabilistic approach to estimating the potential for noncarcinogenic health effects. Instead, the

EXPLANATION OF SAMPLE TABLE FORMAT FOR CANCER RISK ESTIMATES

A sample table format for summarizing cancer risk estimates is provided in Exhibit 8-2. For each baseline risk assessment, at least two summary tables generally would be required: one for current land uses and one for future land uses. In the example provided in Exhibit 8-2, two exposure pathways were determined to contribute to exposure of a nearby residential population under current land use: ingestion of private well water contaminated with benzene and chlordane and ingestion of fish contaminated with chlordane. Moreover, a subset of the population in Area Y was exposed to the maximal well water contamination and consumed more locally caught fish than the remainder of the nearby population.

Values for the chronic daily intake (CDI), averaged over a lifetime, of each contaminant by each exposure pathway would be obtained from a table such as that shown in Exhibit 6-22. The CDI via well water was not adjusted for absorption efficiency because the slope factors for these substances assume ingestion in water and an absorption fraction of 1.0. The CDI for chlordane in fish was not adjusted for vehicle of exposure (i.e., food versus water) because absorption efficiency data were limited, and an absorption fraction of 1.0 was used as a conservative assumption. If, for example, available data had indicated that only 10 percent of chlordane ingested with fish is absorbed, the CDI could have been adjusted downward to 0.000008 mg/kg-day (i.e., 0.00008 mg/kg-day x 0.10 absorption fraction).

Values for the slope factors (SF), weight-of-evidence classification, type of cancer (for Class A carcinogens), reference source of the SF, and basis of the SF (vehicle of administration and absorption efficiency) would be obtained from a table such as that shown in Exhibit 7-3. The chemical-specific risks were calculated from the CDI and SF using the linear low-dose cancer risk equation ($\text{risk} = \text{CDI} \times \text{SF}$). The total pathway risk for ingestion of private well water is the sum of the two chemical-specific risks for that pathway. The total risk estimate for the nearby residential population in area Y is the sum of the cancer risks for the two pathways. Note that it is important to summarize the weight of evidence for the carcinogens contributing most to the total cancer risk estimate; in this example, chlordane, a Class B2 carcinogen, accounted for most of the risk.

EXPLANATION OF SAMPLE TABLE FORMAT FOR CHRONIC HAZARD INDEX ESTIMATES

A sample table format for summarizing chronic hazard index estimates is provided in Exhibit 8-3. For each baseline risk assessment, at least two summary tables generally would be required: one for current land uses and one for future land uses. In the example provided in Exhibit 8-3, two exposure pathways were determined to contribute to exposure of a nearby residential population under current land use: ingestion of private well water contaminated with phenol, nitrobenzene, and cyanide and ingestion of fish contaminated with phenol and methyl ethyl ketone (MEK). Moreover, a subset of the population in Area Y was exposed to the maximal well water contamination and consumed more locally caught fish than the remainder of the nearby population.

Values for the chronic daily intake (CDI), averaged over the period of exposure, of each contaminant by each exposure pathway would be obtained from a table such as that shown in Exhibit 6-22. The CDI via well water was not adjusted for absorption efficiency because the RfDs for these substances are based on ingestion in water and an absorption fraction of 1.0. The CDI for phenol and MEK in fish was not adjusted for vehicle of exposure (i.e., food versus water) because absorption efficiency data were limited, and an absorption fraction of 1.0 was used as a conservative assumption. If, for example, available data had indicated that only 20 percent of MEK ingested with fish is absorbed, the CDI for MEK could have been adjusted downward to 0.001 mg/kg-day (i.e., 0.005 mg/kg-day x 0.20 absorption efficiency).

Values for the RfDs, confidence level in the RfD, critical effect, source of the value, and basis of the RfD (vehicle of administration and absorption efficiency) would be obtained from a table such as that shown in Exhibit 7-2. The chemical-specific hazard quotients are equal to the CDI divided by the RfD. The total pathway hazard index for ingestion of private well water is the sum of the three chemical-specific hazard quotients for that pathway. The total hazard index estimate for the nearby residential population in area Y is the sum of the hazard indices for the two exposure pathways.

Note that it is important to include the noncarcinogenic effects of carcinogenic substances when appropriate reference doses are available. For example, in an actual risk assessment of the chemicals summarized in Exhibit 6-22, the potential noncarcinogenic effects of chlordane should be evaluated and appropriate entries made in tables such as those shown in Exhibits 7-2 and 8-3.

ONE-HIT EQUATION FOR HIGH CARCINOGENIC RISK LEVELS

$$\text{Risk} = 1 - \exp(-\text{CDI} \times \text{SF})$$

where:

Risk = a unitless probability (e.g., 2×10^{-5}) of an individual developing cancer;

exp = the exponential;

CDI = chronic daily intake averaged over 70 years (mg/kg-day); and

potential for noncarcinogenic effects is evaluated by comparing an exposure level over a specified time period (e.g., lifetime) with a reference dose derived for a similar exposure period. This ratio of exposure to toxicity is called a hazard quotient and is described in the box in the opposite column.

The noncancer hazard quotient assumes that there is a level of exposure (i.e., RfD) below which it is unlikely for even sensitive populations to experience adverse health effects. If the exposure level (E) exceeds this threshold (i.e., if E/RfD exceeds unity), there may be concern for potential noncancer effects. As a rule, the greater the value of E/RfD above unity, the greater the level of concern. Be sure, however, not to interpret ratios of E/RfD as statistical probabilities; a ratio of 0.001 does not mean that there is a one in one thousand chance of the effect occurring. Further, it is important to emphasize that the level of concern does not increase linearly as the RfD is approached or exceeded because RfDs do not have equal accuracy or precision and are not based on the same severity of toxic effects. Thus, the slopes of the dose-response curve in excess of the RfD can range widely depending on the substance.

Three exposure durations that will need separate consideration for the possibility of adverse noncarcinogenic health effects are chronic, subchronic, and shorter-term exposures. As

NONCANCER HAZARD QUOTIENT

$$\text{Noncancer Hazard Quotient} = \text{E/RfD}$$

where:

E
= exposure level (or intake);

RfD
= reference dose; and

E and RfD are expressed in the same

guidance for Superfund, chronic exposures for humans range in duration from seven years to a lifetime; such long-term exposures are almost always of concern for Superfund sites (e.g., inhabitants of nearby residences, year-round users of specified drinking water sources). Subchronic human exposures typically range in duration from two weeks to seven years and are often of concern at Superfund sites. For example, children might attend a junior high school near the site for no more than two or three years. Exposures less than two weeks in duration are occasionally of concern at Superfund sites. For example, if chemicals known to be developmental toxicants are present at a site, short-term exposures of only a day or two can be of concern.

8.2.2 AGGREGATE RISKS FOR MULTIPLE SUBSTANCES

At most Superfund sites, one must assess potential health effects of more than one chemical (both carcinogens and other toxicants). Estimating risk or hazard potential by considering one chemical at a time might significantly underestimate the risks associated with simultaneous exposures to several substances. To assess the overall potential for cancer and noncancer effects posed by multiple chemicals, EPA (1986b) has developed *Guidelines for the Health Risk Assessment of Chemical Mixtures* that can also be applied to the case of simultaneous exposures to several chemicals from a variety of sources by more than one exposure pathway. Although the calculation procedures differ for

carcinogenic and noncarcinogenic effects, both sets of procedures assume dose additivity in the absence of information on specific mixtures.

Information on specific mixtures found at Superfund sites is rarely available. Even if such data exist, they are often difficult to use. Monitoring for "mixtures" or modeling the movement of mixtures across space and time present technical problems given the likelihood that individual components will behave differently in the environment (i.e., fate and transport). If data are available on the mixtures present at the site, but are not adequate to support a quantitative evaluation, note the information in the "assumptions" documentation.

Carcinogenic effects. The cancer risk equation described in the box below estimates the incremental individual lifetime cancer risk for simultaneous exposure to several carcinogens and is based on EPA's (1986a,b) risk assessment guidelines. This equation represents an approximation of the precise equation for combining risks which accounts for the joint probabilities of the same individual developing cancer as a consequence of exposure to two or more carcinogens.¹ The difference between the precise equation and the approximation described in the box is negligible for total cancer risks less than 0.1. Thus, the simple additive equation is appropriate for most Superfund risk assessments.

CANCER RISK EQUATION FOR MULTIPLE SUBSTANCES

$$\text{Risk}_T = \sum \text{Risk}_i$$

where:

Risk_T = the total cancer risk, expressed as a unitless probability; and

Risk_i = the risk estimate for the i^{th} substance.

The risk summation techniques described in the box on this page and in the footnote assume that intakes of individual substances are small. They also assume independence of action by the compounds involved (i.e., that there are no synergistic or antagonistic chemical interactions and that all chemicals produce the same effect, i.e., cancer). If these assumptions are incorrect, over- or under-estimation of the actual multiple-substance risk could result.

Calculate a separate total cancer risk for each exposure pathway by summing the substance-specific cancer risks. Resulting cancer risk estimates should be expressed using one significant figure only. Obviously, the total cancer risk for each pathway should not exceed 1. Exhibit 8-2 provides a sample table format for presenting estimated cancer risks for specified exposure pathways in the "Total Pathway Risk" column.

There are several limitations to this approach that must be acknowledged. First, because each slope factor is an upper 95th percentile estimate of potency, and because upper 95th percentiles of probability distributions are not strictly additive, the total cancer risk estimate might become artificially more conservative as risks from a number of different carcinogens are summed. If one or two carcinogens drive the risk, however, this problem is not of concern. Second, it often will be the case that substances with different weights of evidence for human carcinogenicity are included. The cancer risk equation for multiple substances sums all carcinogens equally, giving as much weight to class B or C as to class A carcinogens. In addition, slope factors derived from animal data will be given the same weight as slope factors derived from human data. Finally, the action of two different carcinogens might not be independent. New tools for assessing carcinogen interactions are becoming available, and should be considered in consultation with the RPM (e.g., Arcos *et al.* 1988). The significance of these concerns given the circumstances at a particular site should be discussed and presented with the other information described in Section 8.6.

Noncarcinogenic effects. To assess the overall potential for noncarcinogenic effects posed by more than one chemical, a hazard index (HI) approach has been developed based on EPA's (1986b) *Guidelines*

for *Health Risk Assessment of Chemical Mixtures*. This approach assumes that simultaneous subthreshold exposures to several chemicals could result in an adverse health effect. It also assumes that the magnitude of the adverse effect will be proportional to the sum of the ratios of the subthreshold exposures to acceptable exposures. The hazard index is equal to the sum of the hazard quotients, as described in the box below, where E and the RfD represent the same exposure period (e.g., subchronic, chronic, or shorter-term). When the hazard index exceeds unity, there may be concern for potential health effects. While any single chemical with an exposure level greater than the toxicity value will cause the hazard index to exceed unity, for multiple chemical exposures, the hazard index can also exceed unity even if no single chemical exposure exceeds its RfD.

NONCANCER HAZARD INDEX

$$\text{Hazard Index} = E_1/\text{RfD}_1 + E_2/\text{RfD}_2 + \dots + E_i/\text{RfD}_i$$

where:

E_i = exposure level (or intake) for the i^{th} toxicant;

RfD_i = reference dose for the i^{th} toxicant; and

E and RfD are expressed in the same units and represent the same exposure period (i.e., chronic, subchronic, or shorter-term).

It is important to calculate the hazard index separately for chronic, subchronic, and shorter-term exposure periods as described below. It is also important to remember to include RfDs for the noncancer effects of carcinogenic substances.

- (1) Noncarcinogenic effects -- chronic exposures. For each chronic exposure pathway (i.e., seven year to lifetime exposure), calculate a separate chronic hazard index from the ratios of the chronic daily intake (CDI) to the chronic reference

dose (RfD) for individual chemicals as described in the box below. Exhibit 8-3 provides a sample table format for recording these results in the "Pathway Hazard Index" column.

CHRONIC NONCANCER HAZARD INDEX

$$\text{Chronic Hazard Index} = \text{CDI}_1/\text{RfD}_1 + \text{CDI}_2/\text{RfD}_2 + \dots + \text{CDI}_i/\text{RfD}_i$$

where:

CDI_i = chronic daily intake for the i^{th} toxicant in mg/kg-day, and

RfD_i = chronic reference dose for the i^{th} toxicant in mg/kg-day.

The CDI is identified in Exhibits 6-11 through 6-19 and 6-22 and the RfD is identified in Exhibit 7-2.

- (2) Noncarcinogenic effects -- subchronic exposures. For each subchronic exposure pathway (i.e., two week to seven year exposure), calculate a separate subchronic hazard index from the ratios of subchronic daily intake (SDI) to the subchronic reference dose (RfD_s) for individual chemicals as described in the box on the next page. Exhibit 8-4 provides a sample table format for recording these results in the "Pathway Hazard Index" column. Add only those ratios corresponding to subchronic exposures that will be occurring simultaneously.
- (3) Noncarcinogenic effects -- less than two week exposures. The same procedure may be applied for simultaneous shorter-term exposures to several chemicals. For drinking water exposures, 1- and 10-day Health Advisories can be used as reference toxicity values. Depending on available data, a separate hazard index might also be calculated for developmental toxicants (using RfD_{dt} s), which might cause adverse effects following exposures of only a few days. See

SUBCHRONIC NONCANCER HAZARD INDEX

Subchronic

$$\text{Hazard Index} = \text{SDI}_1/\text{RfD}_{s1} + \text{SDI}_2/\text{RfD}_{s2} + \dots + \text{SDI}_i/\text{RfD}_{si}$$

where:

SDI_i = subchronic daily intake for the i^{th} toxicant in mg/kg-day; and

RfD_{si} = subchronic reference dose for the i^{th} toxicant in mg/kg-day.

Guidelines for the Health Assessment of Suspect Developmental Toxicants (EPA 1986c; EPA 1989) for further guidance.

There are several limitations to this approach that must be acknowledged. As mentioned earlier, the level of concern does not increase linearly as the reference dose is approached or exceeded because the RfDs do not have equal accuracy or precision and are not based on the same severity of effect. Moreover, hazard quotients are combined for substances with RfDs based on critical effects of varying toxicological significance. Also, it will often be the case that RfDs of varying levels of confidence that include different uncertainty adjustments and modifying factors will be combined (e.g., extrapolation from animals to humans, from LOAELs to NOAELs, from one exposure duration to another).

Another limitation with the hazard index approach is that the assumption of dose additivity is most properly applied to compounds that induce the same effect by the same mechanism of action. Consequently, application of the hazard index equation to a number of compounds that are not expected to induce the same type of effects or that do not act by the same mechanism could overestimate the potential for effects, although such an approach is appropriate at a screening level. This possibility is generally not of concern if only one or two substances are responsible for driving the HI above

unity. If the HI is greater than unity as a consequence of summing several hazard quotients of similar value, it would be appropriate to segregate the compounds by effect and by mechanism of action and to derive separate hazard indices for each group.

Segregation of hazard indices. Segregation of hazard indices by effect and mechanism of action can be complex and time-consuming because it is necessary to identify all of the major effects and target organs for each chemical and then to classify the chemicals according to target organ(s) or mechanism of action. This analysis is not simple and should be performed by a toxicologist. If the segregation is not carefully done, an underestimate of true hazard could result. Agency review of particularly complex or controversial cases can be requested of ECAO through the regional risk assessment support staff.

The procedure for recalculating the hazard index by effect and by mechanism of action is briefly described in the box on the next page. If one of the effect-specific hazard indices exceeds unity, consideration of the mechanism of action might be warranted. A strong case is required, however, to indicate that two compounds which produce adverse effects on the same organ system (e.g., liver), although by different mechanisms, should not be treated as dose additive. Any such determination should be reviewed by ECAO.

If there are specific data germane to the assumption of dose-additivity (e.g., if two compounds are present at the same site and it is known that the combination is five times more toxic than the sum of toxicities for the two compounds), then modify the development of the hazard index accordingly. Refer to the EPA (1986b) mixtures guidelines for discussion of a hazard index equation that incorporates quantitative interaction data. If data on chemical interactions are available, but are not adequate to support a quantitative assessment, note the information in the "assumptions" being documented for the site risk assessment.

PROCEDURE FOR SEGREGATION OF HAZARD INDICES BY EFFECT

Segregation of hazard indices requires identification of the major effects of each chemical, including those seen at higher doses than the critical effect (e.g., the chemical may cause liver damage at a dose of 100 mg/kg-day and neurotoxicity at a dose of 250 mg/kg-day). Major effect categories include neurotoxicity, developmental toxicity, reproductive toxicity, immunotoxicity, and adverse effects by target organ (i.e., hepatic, renal, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, and dermal/ocular effects). Although higher exposure levels may be required to produce adverse health effects other than the critical effect, the RfD can be used as the toxicity value for each effect category as a conservative and simplifying step.

INFORMATION SOURCES FOR SEGREGATION OF HAZARD INDICES

Of the available information sources, the ATSDR Toxicological Profiles are well suited in format and content to allow a rapid determination of additional health effects that may occur at exposure levels higher than those that produce the critical effect. Readers should be aware that the ATSDR definitions of exposure durations are somewhat different than EPA's and are independent of species; acute -- up to 14 days; intermediate -- more than 14 days to 1 year; chronic -- greater than one year. IRIS contains only limited information on health effects beyond the critical effect, and EPA criteria documents and HEAs, HEEPs, and HEEDs may not systematically cover all health effects observed at doses higher than those associated with the most sensitive effects.

8.3 COMBINING RISKS ACROSS EXPOSURE PATHWAYS

This section gives directions for combining the multi-chemical risk estimates across exposure pathways and provides guidance for determining when such aggregation is appropriate.

In some Superfund site situations, an individual might be exposed to a substance or combination of substances through several pathways. For example, a single individual might be exposed to substance(s) from a hazardous waste site by consuming contaminated drinking water from a well, eating

contaminated fish caught near the site, and through inhalation of dust originating from the site. The total exposure to various chemicals will equal the sum of the exposures by all pathways. One should not automatically sum risks from all exposure pathways evaluated for a site, however. The following subsections describe how to identify exposure pathways that should be combined and, for these, how to sum cancer risks and noncancer hazard indices across multiple exposure pathways.

8.3.1 IDENTIFY REASONABLE EXPOSURE PATHWAY COMBINATIONS

There are two steps required to determine whether risks or hazard indices for two or more pathways should be combined for a single exposed individual or group of individuals. The first is to identify reasonable exposure pathway combinations. The second is to examine whether it is likely that the same individuals would consistently face the "reasonable maximum exposure" (RME) by more than one pathway.

Identify exposure pathways that have the potential to expose the same individual or subpopulation at the key exposure areas evaluated in the exposure assessment, making sure to consider areas of highest exposure for each pathway for both current and future land-uses (e.g., nearest downgradient well, nearest downwind receptor). For each pathway, the risk estimates and hazard indices have been developed for a particular exposure area and time period; they do not necessarily apply to other locations or time periods. Hence, if two pathways do not affect the same individual or subpopulation, neither pathway's individual risk estimate or hazard index affects the other, and risks should not be combined.

Once reasonable exposure pathway combinations have been identified, it is necessary to examine whether it is likely that the same individuals would consistently face the RME as estimated by the methods described in Chapter 6. Remember that the RME estimate for each exposure pathway includes many conservative and upper-bound parameter values and assumptions (e.g., upper 95th confidence limit on amount of water ingested, upper-bound duration of occupancy of a single residence). Also,

some of the exposure parameters are not predictable in either space or time (e.g., maximum downwind concentration may shift compass direction, maximum ground-water plume concentration may move past a well). For real world situations in which contaminant concentrations vary over time and space, the same individual may or may not experience the RME for more than one pathway over the same period of time. One individual might face the RME through one pathway, and a different individual face the RME through a different pathway. Only if you can explain why the key RME assumptions for more than one pathway apply to the same individual or subpopulation should the RME risks for more than one pathway be combined.

In some situations, it may be appropriate to combine one pathway's RME risks with other pathways' risk estimates that have been derived from more typical exposure parameter values. In this way, resulting estimates of combined pathway risks may better relate to RME conditions.

If it is deemed appropriate to sum risks and hazard indices across pathways, the risk assessor should clearly identify those exposure pathway combinations for which a total risk estimate or hazard index is being developed. The rationale supporting such combinations should also be clearly stated. Then, using the methods described in Sections 8.3.2 and 8.3.3, total cancer risk estimates and hazard indices should be developed for the relevant exposure areas and individuals (or subpopulations). For example, Exhibits 8-2 and 8-3 illustrate the combination of cancer risk estimates and chronic noncancer hazard indices, respectively, for a hypothetical nearby residential population exposed to contaminants from a site by two exposure pathways: drinking contaminated ground water from private wells and ingestion of contaminated fish caught in the local river. In this hypothetical example, it is "known" that the few families living next to the site consume more locally caught fish than the remaining community and have the most highly contaminated wells of the area.

The following two subsections describe how to sum risks and hazard indices for multiple exposure pathways for carcinogenic and noncarcinogenic substances, respectively.

8.3.2 SUM CANCER RISKS

First, sum the cancer risks for each exposure pathway contributing to exposure of the same individual or subpopulation. For Superfund risk assessments, cancer risks from various exposure pathways are assumed to be additive, as long as the risks are for the same individuals and time period (i.e., less-than-lifetime exposures have all been converted to equivalent lifetime exposures). This summation is described in the box below. The sample table format given in Exhibit 8-2 provides a place to record the total cancer risk estimate.

CANCER RISK EQUATION FOR MULTIPLE PATHWAYS

Total Exposure Cancer Risk =

$$\begin{aligned} &\text{Risk}(\text{exposure pathway}_1) + \\ &\text{Risk}(\text{exposure pathway}_2) + \dots + \\ &\text{Risk}(\text{exposure pathway}_i) \end{aligned}$$

As described in Section 8.2.2, although the exact equation for combining risk probabilities includes terms for joint risks, the difference between the exact equation and the approximation described above is negligible for total cancer risks of less than 0.1.

8.3.3 SUM NONCANCER HAZARD INDICES

To assess the overall potential for noncarcinogenic effects posed by several exposure pathways, the total hazard index for each exposure duration (i.e., chronic, subchronic, and shorter-term) should be calculated separately. This equation is described in the box on the next page. The sample table format given in Exhibit 8-3 provides a place to record the total exposure hazard index for chronic exposure durations.

When the total hazard index for an exposed individual or group of individuals exceeds unity, there may be concern for potential noncancer health effects. For multiple exposure pathways, the hazard index can exceed unity even if no single exposure pathway hazard index exceeds unity. If the total hazard index exceeds unity and if combining exposure pathways has resulted in combining hazard indices based on different chemicals, one may need

HAZARD INDEX EQUATION FOR MULTIPLE PATHWAYS

Total Exposure Hazard Index =

Hazard Index(exposure pathway₁) +
Hazard Index(exposure pathway₂) + +
Hazard Index(exposure pathway_i)

where:

Total Exposure Hazard Index is calculated separately for chronic, subchronic, and shorter-term exposure periods.

to consider segregating the contributions of the different chemicals according to major effect (see Section 8.2.2.).

8.4 ASSESSMENT AND PRESENTATION OF UNCERTAINTY

This section discusses practical approaches to assessing uncertainty in Superfund site risk assessments and describes ways to present key information bearing on the level of confidence in quantitative risk estimates for a site. The risk measures used in Superfund site risk assessments usually are not fully probabilistic estimates of risk, but conditional estimates given a considerable number of assumptions about exposure and toxicity (e.g., risk given a particular future land-use). Thus, it is important to fully specify the assumptions and uncertainties inherent in the risk assessment to place the risk estimates in proper perspective. Another use of uncertainty characterization can be to identify areas where a moderate amount of additional data collection might significantly improve the basis for selection of a remedial alternative.

Highly quantitative statistical uncertainty analysis is usually not practical or necessary for Superfund site risk assessments for a number of reasons, not the least of which are the resource requirements to collect and analyze site data in such a way that the results can be presented as valid

probability distributions. As in all environmental risk assessments, it already is known that uncertainty about the numerical results is generally large (i.e., on the range of at least an order of magnitude or greater). Consequently, it is more important to identify the key site-related variables and assumptions that contribute most to the uncertainty than to precisely quantify the degree of uncertainty in the risk assessment. Thus, the focus of this section is on qualitative/semi-quantitative approaches that can yield useful information to decision-makers for a limited resource investment.

There are several categories of uncertainties associated with site risk assessments. One is the initial selection of substances used to characterize exposures and risk on the basis of the sampling data and available toxicity information. Other sources of uncertainty are inherent in the toxicity values for each substance used to characterize risk. Additional uncertainties are inherent in the exposure assessment for individual substances and individual exposures. These uncertainties are usually driven by uncertainty in the chemical monitoring data and the models used to estimate exposure concentrations in the absence of monitoring data, but can also be driven by population intake parameters. Finally, additional uncertainties are incorporated in the risk assessment when exposures to several substances across multiple pathways are summed.

The following subsections describe how to summarize and discuss important site-specific exposure uncertainties and the more general toxicity assessment uncertainties.

8.4.1 IDENTIFY AND EVALUATE IMPORTANT SITE-SPECIFIC UNCERTAINTY FACTORS

Uncertainties in the exposure assessment typically include most of the site-specific uncertainties inherent in risk characterization, and thus are particularly important to summarize for each site. In risk assessments in general, and in the exposure assessment in particular, several sources of uncertainty need to be addressed: (1) definition of the physical setting, (2) model applicability and assumptions, (3) transport, fate, and exposure parameter values, and (4) tracking uncertainty, or how uncertainties are magnified through the various steps

of the assessment. Some of these sources of uncertainty can be quantified while others are best addressed qualitatively.

Definition of the physical setting. The initial characterization of the physical setting that defines the risk assessment for a Superfund site involves many professional judgments and assumptions. These include definition of the current and future land uses, identification of possible exposure pathways now and in the future, and selection of substances detected at the site to include in the quantitative risk assessment. In Superfund risk assessments, particular attention should be given to the following aspects of the definition of the physical setting.

- Likelihood of exposure pathways and land uses actually occurring. A large part of the risk assessment is the estimation of cancer risks or hazard indices that are conditional on the existence of the exposure conditions analyzed; e.g., if a residential development is built on the site 10 years from now, the health risks associated with contaminants from the site would be X. It is important to provide the RPM or other risk manager with information related to the likelihood that the assumed conditions will occur to allow interpretation of a conditional risk estimate in the proper context. For example, if the probability that a residential development would be built on the site 10 or 50 years from now is very small, different risk management decisions might be made than if the probability is high. Present the information collected during scoping and for the exposure assessment that will help the RPM to identify the relative likelihood of occurrence of each exposure pathway and land-uses, at least qualitatively (e.g., institutional land-use controls, zoning, regional development plans).
- The chemicals not included in the quantitative risk estimate as a consequence of missing information on health effects or lack of quantitation in the chemical analysis may represent a significant source of uncertainty in the final risk estimates. If chemicals with known health effects were

eliminated from the risk assessment on the basis of concentration or frequency of detection, one should now review and confirm whether or not any of the chemicals previously eliminated should actually be included. For substances detected at the site, but not included in the quantitative risk assessment because of data limitations, discuss possible consequences of the exclusion on the risk assessment.

A checklist of uncertainty factors related to the definition of the physical setting is described in the box below.

LIST PHYSICAL SETTING DEFINITION UNCERTAINTIES

- For chemicals not included in the quantitative risk assessment, describe briefly:
 - reason for exclusion (e.g., quality control), and
 - possible consequences of exclusion on risk assessment (e.g., because of widespread contamination, underestimate of risk).
- For the current land uses describe:
 - sources and quality of information, and
 - qualitative confidence level.
- For the future land uses describe:
 - sources and quality of information, and
 - information related to the likelihood of occurrence.
- For each exposure pathway, describe why pathway was selected or not selected for evaluation (i.e., sample table format from Exhibit 6-8).
- For each combination of pathways, describe any qualifications regarding the selection of exposure pathways considered to contribute to exposure of the same individual or group of individuals over the same period of time.

Model applicability and assumptions. There is always some doubt as to how well an exposure model or its mathematical expression (e.g., ground-water transport model) approximates the true relationships between site-specific environmental conditions. Ideally, one would like to use a fully validated model that accounts for all the known complexities in the parameter interrelationships for each assessment. At present, however, only simple, partially validated models are available and commonly used. As a consequence, it is important to identify key model assumptions (e.g., linearity, homogeneity, steady-state conditions, equilibrium) and their potential impact on

the risk estimates. In the absence of field data for model validation, one could perform a limited sensitivity analysis (i.e., vary assumptions about functional relationships) to indicate the magnitude of uncertainty that might be associated with model form. At a minimum, one should list key model assumptions and indicate potential impact of each on risk with respect to both direction and magnitude, as shown in the box below. A sample table format is presented in Exhibit 6-21 of Chapter 6.

CHARACTERIZE MODEL UNCERTAINTIES	
•	List/summarize the key model assumptions.
•	Indicate the potential impact of each on risk:
	- direction (i.e., may over- or underestimate risk); and
	- magnitude (e.g., order of magnitude).

Parameter value uncertainty. During the course of a risk assessment, numerous parameter values are included in the calculations of chemical fate and transport and human intake. A first step in characterizing parameter value uncertainty in the baseline risk assessment is to identify the key parameters influencing risk. This usually can be accomplished by expert opinion or by an explicit sensitivity analysis. In a sensitivity analysis, the values of parameters suspected of driving the risks are varied and the degree to which changes in the input variables result in changes in the risk estimates are summarized and compared (e.g., the ratio of the change in output to the change in input). It is important to summarize the uncertainty associated with key parameters, as described below.

- Significant site data gaps might have required that certain parameter values be assumed for the risk assessment. For example, no information on the frequency with which individuals swim in a nearby stream might be available for a site, and an assumed frequency and duration of swimming events based on a national average could have driven the exposure estimate for this pathway.

- Significant data uncertainties might exist for other parameters, for example, whether or not the available soil concentration measurements are representative of the true distribution of soil contaminant concentrations.

Tracking uncertainty. Ideally, one would like to carry through the risk assessment the uncertainty associated with each parameter in order to characterize the uncertainty associated with the final risk estimates. A more practical approach for Superfund risk assessments is to describe qualitatively how the uncertainties might be magnified or biased through the risk models used. General quantitative, semi-quantitative, and qualitative approaches to uncertainty analysis are described below.

Quantitative approach. Only on the rare occasions that an RPM may indicate the need for a quantitative uncertainty analysis should one be undertaken. As mentioned earlier, a highly quantitative statistical uncertainty analysis is usually not practical or necessary for Superfund sites.

If a quantitative analysis is undertaken for a site, it is necessary to involve a statistician in the design and interpretation of that analysis. A quantitative approach to characterizing uncertainty might be appropriate if the exposure models are simple and the values for the key input parameters are well known. In this case, the first step would be to characterize the probability distributions for key input parameter values (either using measured or assumed distributions). The second step would be to propagate parameter value uncertainties through the analysis using analytic (e.g., first-order Taylor series approximation) or numerical (e.g., Monte Carlo simulation) methods, as appropriate. Analytic methods might be feasible if there are a few parameters with known distributions and linear relationships. Numerical methods (e.g., Monte Carlo simulation) can be suitable for more complex relationships, but must be done on a computer and can be resource intensive even with time-saving techniques (e.g., Latin Hypercube sampling).

Two common techniques of propagating uncertainty are first-order analyses and Monte Carlo simulations. First-order analysis is based on the assumption that the total variance of a model output variable is a function of the variances of the individual model input variables and the sensitivity of the output variable to changes in input variables. The sensitivity of the output variable is defined by the first derivative of the function or model, which can be generated analytically or numerically. A Monte Carlo simulation estimates a distribution of exposures or risk by repeatedly solving the model equation(s). The probability distribution for each variable in the model must be defined. The computer selects randomly from each distribution every time the equation is solved. From the resulting output distribution of exposures or risk, the assessor can identify the value corresponding to any specified percentile (e.g., the 95th percentile in the exposure distribution).

These quantitative techniques require definition of the distribution of all input parameters and knowledge of the degree of dependence (i.e., covariance) among parameters. The value of first-order analyses or Monte Carlo simulations in estimating exposure or risk probability distributions diminishes sharply if one or more parameter value distributions are poorly defined or must be assumed. These techniques also become difficult to document and to review as the number of model parameters increases. Moreover, estimating a probability distribution for exposures and risks can lead one into a false sense of certainty about the analysis. Even in the most comprehensive analyses, it will generally be true that not all of the sources of uncertainty can be accounted for or all of the parameter codependencies recognized. Therefore, in addition to documenting all input distributions and covariances, it is very important to identify all of the assumptions and incomplete information that have not been accounted for in the quantitative uncertainty analysis (e.g., likelihood that a particular land use will occur) when presenting the results.

References describing numerical methods of propagating uncertainty through a risk analysis include Burmaster and von Stackelberg (1988), Hoffman and Gardner (1983), Iman and Helton (1988), and NRC (1983). References describing analytic methods of tracking uncertainty include

Hoffman and Gardner (1983), NRC (1983), Downing *et al.* (1985), and Benjamin and Cornell (1970).

Semi-quantitative approach. Often available data are insufficient to fully describe parameter distributions, but are sufficient to describe the potential range of values the parameters might assume. In this situation, sensitivity analyses can be used to identify influential model input variables and to develop bounds on the distribution of exposure or risk. A sensitivity analysis can estimate the range of exposures or risk that result from combinations of minimum and maximum values for some parameters and mid-range values for others. The uncertainty for an assessment of this type could be characterized by presenting the ranges of exposure or risk generated by the sensitivity analysis and by describing the limitations of the data used to estimate plausible ranges of model input variables (EPA 1985).

Qualitative approach. Sometimes, a qualitative approach is the most practical approach to describing uncertainty in Superfund site risk assessments given the use of the information (e.g., identifying areas where the results may be misleading). Often the most practical approach to characterizing parameter uncertainty will be to develop a quantitative or qualitative description of the uncertainty for each parameter and to simply indicate the possible influence of these uncertainties on the final risk estimates given knowledge of the models used (e.g., a specific ground-water transport model). A checklist of uncertainty factors related to the definition of parameters is described in the box on page 8-22. A sample table format is provided in Exhibit 6-21 of Chapter 6.

Consider presentation of information on key parameter uncertainties in graphic form to illustrate clearly to the RPM or other risk managers the significance of various assumptions. For example, Exhibit 8-5 plots assumptions regarding contaminated fish ingestion and resulting impacts on the cancer risk estimate for this exposure pathway. Exhibit 8-6 illustrates the significance of these same assumptions for the hazard index estimates for contaminated fish consumption. Additionally, maps showing isopleths of risks resulting from modeled air exposures such as emissions near the site may assist the RPM or risk manager in visualizing the significance of current or future site risks for a community.

CHARACTERIZE FATE AND TRANSPORT AND EXPOSURE PARAMETER UNCERTAINTIES

- List all key exposure assessment parameters (e.g., infiltration rate, exposure duration, bioconcentration factors, body weight).
- List the value used for each parameter and rationale for its selection.
- Describe the measured or assumed parameter value distributions, if possible, considering:
 - total range;
 - shape of distribution, if known (e.g., log-normal);
 - mean (geometric or arithmetic) + standard deviation; and/or
 - specific percentiles (e.g., median, 95th).
- Quantify the uncertainty of statistical values used in the risk assessment (e.g., standard error of the mean) or data gaps and qualifiers.
- Describe potential direction and magnitude of bias in risk estimate resulting from assumptions or data gaps (see Exhibit 6-21).

8.4.2 IDENTIFY/EVALUATE TOXICITY ASSESSMENT UNCERTAINTY FACTORS

For substances that contribute most to the estimates of cancer risk and noncancer hazard indices, summarize the uncertainty inherent in the toxicity values for the durations of exposure assessed. Some of the information (e.g., weight of evidence for potential human carcinogens, uncertainty adjustments for noncancer toxicity values) has already been recorded in the sample table formats provided in Exhibits 8-2 through 8-4. Other information will be developed during the toxicity assessment itself (see Chapter 7). The box on page 8-24 provides a checklist of uncertainties that apply to most toxicity assessments.

Multiple substance exposure uncertainties. Uncertainties associated with summing risks or hazard indices for several substances are of particular concern in the risk characterization step. The assumption of dose additivity ignores possible

synergisms or antagonisms among chemicals, and assumes similarity in mechanisms of action and metabolism. Unfortunately, the data available to assess interactions quantitatively are generally lacking. In the absence of adequate information, EPA guidelines indicate that carcinogenic risks should be treated as additive and that noncancer hazard indices should also be treated as additive. These assumptions are made to help prevent an underestimation of cancer risk or potential noncancer health effects at a site.

Be sure to discuss the availability of information concerning potential antagonistic or synergistic effects of chemicals for which cancer risks or hazard indices have been summed for the same exposed individual or subpopulations. On the basis of available information concerning target organ specificity and mechanism of action, indicate the degree to which treating the cancer risks as additive may over- or under-estimate risk. If only qualitative information is available concerning potential interactions or dose-additivity for the noncarcinogenic substances, discuss whether the information indicates that hazard indices may have been over- or under-estimated. This discussion is particularly important if the total hazard index for an exposure point is slightly below or slightly above unity, or if the total hazard index exceeds unity and the effect-specific hazard indices are less than unity, and if the uncertainty is likely to significantly influence the risk management decision at the site.

8.5 CONSIDERATION OF SITE- SPECIFIC HUMAN STUDIES

This section describes how to compare the results of the risk characterization step with ATSDR health assessments and other site-specific human studies that might be available. The first subsection outlines how to compare an ATSDR health assessment for the site with the risk results summarized in the previous sections (Sections 8.2, 8.3, and 8.4). The second subsection discusses when epidemiological or health studies might provide useful information for assessing exposures and health risks associated with contaminants from a site.

CHARACTERIZE TOXICITY ASSESSMENT UNCERTAINTIES

For each substance carried through the quantitative risk assessment, list uncertainties related to:

- qualitative hazard findings (i.e., potential for human toxicity);
- derivation of toxicity values, e.g.,
 - human or animal data,
 - duration of study (e.g., chronic study used to set subchronic RfD), and
 - any special considerations;
- the potential for synergistic or antagonistic interactions with other substances affecting the same individuals; and
- calculation of lifetime cancer risks on the basis of less-than-lifetime exposures.

For each substance not included in the quantitative risk assessment because of inadequate toxicity information, list:

- possible health effects; and
- possible consequences of exclusion on final risk estimates.

8.5.1 COMPARE WITH ATSDR HEALTH ASSESSMENT

ATSDR health assessments were defined and compared to the RI/FS risk assessment in Section 2.2.2. As of 1989, preliminary ATSDR health assessments should be completed before the RI/FS risk assessment is initiated and therefore should be available to the risk assessor as early as "scoping." The steps for comparing the preliminary ATSDR health assessment with the baseline risk assessment are outlined below.

Review again the ATSDR health assessment findings and conclusions. These will be largely qualitative in nature. If the ATSDR health assessment identifies exposure pathways or chemicals of concern that have not been included in the RI/FS baseline risk assessment, describe the information supporting the decision not to include these parameters. If there are differences in the qualitative conclusions of the health assessment and

the quantitative conclusions of the baseline risk assessment, explain the differences, if possible, and discuss their implications.

8.5.2 COMPARE WITH OTHER AVAILABLE SITE-SPECIFIC EPIDEMIOLOGICAL OR HEALTH STUDIES

For most Superfund sites, studies of human exposure or health effects in the surrounding population will not be available. However, if controlled epidemiological or other health studies have been conducted, perhaps as a consequence of the preliminary ATSDR health assessment or other community involvement, it is important to include this information in the baseline risk assessment as appropriate. However, not all such studies provide meaningful information in the context of Superfund risk assessments.

One can determine the availability of other epidemiological or health studies for populations potentially exposed to contaminants from the site by contacting the ATSDR Regional Representative, the Centers for Disease Control in Atlanta, Georgia, and state and local health agencies as early in the risk assessment process as possible. It is important to avoid use of anecdotal information or data from studies that might include a significant bias or confounding factor, however. Isolated reports of high body levels of substances that are known to be present at the site in a few individuals living near the site are not sufficient evidence to confirm the hypothesis that these individuals have received significant exposures from the site. Nor can isolated reports of disease or symptoms in a few individuals living near the site be used to confirm the hypothesis that the cause of the health effects in these individuals was exposure to contamination from the site. A trained epidemiologist should review any available studies in order to identify possible study limitations and implications for site risk findings. The small populations and variable exposures predominating at most Superfund sites will make it extremely difficult to detect site-related effects using epidemiological techniques.

If site-specific health or exposure studies have been identified and evaluated as adequate, one should incorporate the study findings into the overall

risk characterization to strengthen the conclusions of the risk assessment (e.g., the risk assessment predicts elevated blood lead levels and the human exposure study documented elevated blood lead levels only among those exposed to ground water contaminated by the site). Because of the generally large and different types of uncertainties associated with the risk assessment and actual health studies, a qualitative, not quantitative, comparison between the two types of studies is generally warranted. Areas of agreement and disagreement between the health study(ies) and the risk assessment should be described and factors that might contribute to any disagreement discussed.

8.6 SUMMARIZATION AND PRESENTATION OF THE BASELINE RISK CHARACTERIZATION RESULTS

This section provides guidance on interpreting and presenting the risk characterization results. The results of the baseline evaluation should not be taken as a characterization of absolute risk. An important use of the risk and hazard index estimates is to highlight potential sources of risk at a site so that they may be dealt with effectively in the remedial process. It is the responsibility of the risk assessment team to develop conclusions about the magnitude and kinds of risk at the site and the major uncertainties affecting the risk estimates. It is not the responsibility of the risk assessment team to evaluate the significance of the risk in a program context, or whether and how the risk should be addressed, which are risk management decisions.

The ultimate user of the risk characterization results will be the RPM or other risk manager for the site. This section therefore outlines a presentation of material that is designed to assist the risk manager in using risk information to reach site-specific decisions.

8.6.1 SUMMARIZE RISK INFORMATION IN TEXT

The final discussion of the risk characterization results is a key component of the risk characterization. The discussion provides a means

of placing the numerical estimates of risk and hazard in the context of what is known and what is not known about the site and in the context of decisions to be made about selection of remedies. At a minimum, the discussion should include:

- confidence that the key site-related contaminants were identified and discussion of contaminant concentrations relative to background concentration ranges;
- a description of the various types of cancer and other health risks present at the site (e.g., liver toxicity, neurotoxicity), distinguishing between known effects in humans and those that are predicted to occur based on animal experiments;
- level of confidence in the quantitative toxicity information used to estimate risks and presentation of qualitative information on the toxicity of substances not included in the quantitative assessment;
- level of confidence in the exposure estimates for key exposure pathways and related exposure parameter assumptions;
- the magnitude of the cancer risks and noncancer hazard indices relative to the Superfund site remediation goals in the NCP (e.g., the cancer risk range of 10^{-4} to 10^{-7} and noncancer hazard index of 1.0);
- the major factors driving the site risks (e.g., substances, pathways, and pathway combinations);
- the major factors reducing the certainty in the results and the significance of these uncertainties (e.g., adding risks over several substances and pathways);
- exposed population characteristics; and
- comparison with site-specific health studies, when available.

In addition, if the size of the potentially exposed population is large, the presentation of population numbers may be of assistance to the RPM, especially in evaluating risks in the context of current land use.

Individual risk estimates based on the reasonable maximum exposure (RME) should not be presented as representative of a broadly defined population, however.

8.6.2 SUMMARIZE RISK INFORMATION IN TABLES

A tabular summary of the cancer risks and noncancer hazard indices should be prepared for all exposure pathways and land uses analyzed and for all substances carried through the risk assessment. These tables must be accompanied by explanatory text, as described in the previous section, and should not be allowed to stand alone as the entire risk characterization. The sample table formats presented in Chapter 6 and in Exhibits 8-2 to 8-6 provide basic summary formats. Exhibits 8-7 and 8-8 provide examples of optional presentations that might assist in visualization of the risk assessment results. These bar graphs present the baseline cancer risk estimates and noncancer hazard indices, respectively, by pathway for an identified subpopulation near the site. The stacked bars in Exhibit 8-8 allow the reader to immediately identify the pathway(s) contributing most to the total hazard index as well as

identify the substances driving the indices in each pathway. Reference levels are also provided (e.g., hazard index of 1.0). Exhibits 8-5 and 8-6 introduced in Section 8.4.1 provide examples of figures that could help the RPM or other risk manager visualize the impact of various assumptions and uncertainties on the final risk or hazard index estimate. In addition, graphics relating risk level (or magnitude of hazard index) to concentrations of substances in environmental media and cost of "treatment" could allow the RPM or other risk manager to weigh the benefits of various remedial alternatives more easily. Examples of the last type of graphics are presented in Part C of this manual.

In a few succinct concluding paragraphs, summarize the results of the risk characterization step. It is the responsibility of the risk assessment team members, who are familiar with all steps in the site risk assessment, to highlight the major conclusions of the risk assessment. The discussion should summarize both the qualitative and the quantitative findings of cancer risks and noncancer hazards, and properly qualify these by mention of major assumptions and uncertainties in the assessment.

ENDNOTE FOR CHAPTER 8

1. The probability of an individual developing cancer following exposure to more than one carcinogen is the probability of developing cancer from *at least one* of the carcinogens. For two carcinogens, the precise equation for estimating this probability is $\text{risk}_1 + \text{risk}_2 - \text{probability}(\text{risk}_1, \text{risk}_2)$ where the latter term is the joint probability of the two risks occurring in the same individual. If the risk to agent 1 is distributed in the population independently of the risk to agent 2, the latter term would equal $(\text{risk}_1)(\text{risk}_2)$. This equation can be expanded to evaluate risks from more than two substances.

REFERENCES FOR CHAPTER 8

- Arcos, J., Woo, Y.T., and Lai, D. 1988. Data Base on Binary Combination Effects of Chemical Carcinogens. Environ. Carcino. Revs. [J. Environ. Sci. Health Pt. C] 6:1-150.
- Benjamin, J.R. and C.A. Cornell. 1970. Probability, Statistics, and Decision-making for Civil Engineers. McGraw Hill. New York.
- Burmester, D.E. and K. von Stackelberg. 1988. A New Method for Uncertainty and Sensitivity Analysis in Public Health Risk Assessments at Hazardous Waste Sites Using Monte Carlo Techniques in a Spreadsheet. Pages 550-556 in Superfund '88, Proceedings of the 9th National Conference. Washington, D.C. Sponsored by the Hazardous Materials Control Research Institute.
- Downing, D. J., Gardner, R. H., and Hoffman, F. O. 1985. Response Surface Methodologies for Uncertainty Analysis in Assessment Models. Technometrics 27:151-163.
- Environmental Protection Agency (EPA). 1985. Methodology for Characterization of Uncertainty in Exposure Assessments. Prepared by Research Triangle Institute. NTIS: PB85-240455.
- Environmental Protection Agency (EPA). 1986a. Guidelines for Carcinogen Risk Assessment. 51 Federal Register 33992 (September 24, 1986).
- Environmental Protection Agency (EPA). 1986b. Guidelines for the Health Risk Assessment of Chemical Mixtures. 51 Federal Register 34014 (September 24, 1986).
- Environmental Protection Agency (EPA). 1986c. Guidelines for the Health Assessment of Suspect Developmental Toxicants. 51 Federal Register 34028 (September 24, 1986).
- Environmental Protection Agency (EPA). 1989. Proposed Amendments to the Guidelines for the Health Assessment of Suspect Developmental Toxicants. 54 Federal Register 9386 (March 6, 1989).
- Hoffman, F. O. and R. H. Gardner. 1983. Evaluation of Uncertainties in Radiological Assessment Models. In: Radiological Assessment, A Textbook on Environmental Dose Analysis. Till, J. E., and H.R. Meyer, (eds.). Prepared for Office of Nuclear Reactor Regulation, U.S. Nuclear Regulatory Commission. Washington, DC. NRC FIN B0766. NUREG/CR-3332.
- Iman, R. L. and J. C. Helton. 1988. An Investigation of Uncertainty and Sensitivity Analysis Techniques for Computer Models. Risk Analysis 8:71-90.
- IRIS. Integrated Risk Information System (data base). 1989. U.S. Environmental Protection Agency, Office of Research and Development.
- Metcalf, D.R. and J.W. Pegram. 1981. Uncertainty Propagation in Probabilistic Risk Assessment: A Comparative Study. Transactions of the American Nuclear Society 38:483-484.
- Nuclear Regulatory Commission (NRC). 1983. PRA Procedures Guide - A Guide to the Performance of Probabilistic Risk Assessments for Nuclear Power Plants. Office of Nuclear Regulatory Research, Washington, D.C. NUREG/CR-2300. Vol. 2.
- Vesely, W. E. and D. M. Rasmuson. Uncertainties in Nuclear Probabilistic Risk Analysis. Risk Analysis 4:313-322.
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